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MULTIPLE LYMPHO-SARCOMATA,

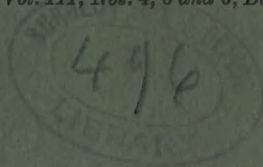
WITH A REPORT OF TWO CASES.

By SIMON FLEXNER, M.D.

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*presented by the author*

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## MULTIPLE LYMPHO-SARCOMATA, WITH A REPORT OF TWO CASES.

A CONTRIBUTION TO THE INFECTIOUS NATURE OF LYMPHO-  
SARCOMA.

BY SIMON FLEXNER, M. D.

Cases of lympho-sarcoma are not of very unusual occurrence. The disease, which affects apparently all classes of people, without distinction of age or sex, is now so generally recognized that the addition of a few cases to our records is not necessarily a matter of special interest. Since, however, the etiology of this affection is still enveloped in such obscurity, we cannot afford to pass by any instance which may be calculated to aid us, however little, in the solution of this difficult problem. We think we have been fortunate in meeting with two cases of the disease both of which presented unusual features, and we have endeavored to study their pathological histology in detail. This communication is intended to give the results of this study, together with a review of the subject of lympho-sarcoma in general, and the conclusions to which we have been led.

### CASE 1.—CLINICAL HISTORY.

Peter Slert, age 27, was admitted into the Johns Hopkins Hospital, in the service of Dr. Osler, on the 12th of August, 1891. The history of the patient is briefly as follows: His father at the age of 56 had died suddenly from a cause unknown to the patient. His mother was said to have died young. At the time of his admission he had two brothers and two sisters living and apparently in good health. His own health had always been good up to the present illness, excepting an attack of malaria (?) ten or twelve years before. He denied having had gonorrhœa and syphilis. He drank moderately; his occupation was that of a stevedore.

In April of the same year (1891) he had gone to Pittsburgh, Pa., where he remained two weeks. He returned to Baltimore in May.



He dated his illness from about this time, attributing it to the water he drank while in Pittsburgh.

The present attack came on with diarrhoea, and two weeks later micturition became painful. He had four or five stools a day; the diarrhoea stopped two days before his admission. Vomiting set in at this time and was intractable; every time he took a drink of water he would be seized with it, and he complained of a peculiar sensation as if something solid remained behind. He had a heavy feeling in the epigastrium, but no sharp pain. Micturition was still painful at this time. He said that he had not slept for some nights prior to his entrance to the Hospital. He had been constipated for the last few days and had had no passage from his bowels since the cessation of the diarrhoea. He complained of cramps in the calves of his legs.

*Status Præsens.*—Patient is emaciated, very sallow, his skin is harsh and dry, and he has a moderate anæmia. The tongue is red, dry and inclined to be glazed; on the dorsum, pointed. Pupils are equal and react to light. Temperature normal and subnormal; pulse 98, small in volume and regular. Respiration 20.

Chest and heart normal. The abdomen is retracted, tympanitic, tender on pressure, particularly in lower zone and iliac regions. No tumor palpable; no special tenderness anywhere. No spots, nor rash. Spleen not palpable, nor is dullness increased. Liver normal. Rectum: the mucous membrane feels a little rough perhaps; otherwise normal. No glandular enlargement anywhere over the body, so far as can be determined.

*August 14th.* Patient has had much vomiting; especially rejects milk. He complains of abdominal pain, which is relieved by turpentine stupes. His temperature varies from 97° to 99°. Pulse good; 96 to the minute.

*August 16th.* Patient's condition about the same. He has had one stool, consisting of a dark green liquid without blood or mucus; it was not examined microscopically.

*August 17th.* Patient became suddenly worse at about 8.30 P. M., when he got out of bed, fell on the floor, and was put back to bed very much exhausted and excited. He continued to vomit stimulants and nourishments, and at 11.30 was very low, pulse almost imperceptible at the wrist, he gasped for breath, but was revived by hypodermics of ether. At 4.50 A. M. he went into a collapse and died at 5.45.

AUTOPSY.

The autopsy was made 8 hours after death by Prof. Welch.

*Exterior.* Body much emaciated; cachectic appearance of facies. Rigor mortis in both upper and lower extremities.

*Interior.* There is very little subcutaneous adipose tissue. In the omentum there is likewise little fat. The peritoneal cavity is dry and free from adhesions, except at the left border of the omentum. Diaphragm on the right side at the fifth intercostal space; on the left side at the sixth rib. Slight ossification of the costal cartilages. The pleuræ free from adhesions, except at the base of the right lung, over the diaphragm. Pleural and pericardial cavities are dry.

*Heart.* The right cavities contain dark red fluid and coagulated blood and some decolorized clots. Left ventricle is well contracted, the valves are normal. Heart cavities and walls are normal, with the possible exception of the left ventricle, which may be slightly hypertrophied. Thickness of the left ventricle, 15 millimeters; of the right, 4 millimeters. Inner circumference of the aorta just above the valves, 5 centimeters.

*Lungs.* They are retracted, dry and slightly emphysematous at the margins and apices. In the left posterior lobe is a calcareous nodule beneath the pleura, the size of a pea. The lower half of the right upper lobe is very œdematous and hyperæmic; it is swollen, but the lung substance floats in water. A similar condition is present in the upper portion of the right lower lobe. These areas resemble beginning flabby hepatization or pneumonia.

*Spleen.* Normal, free from adhesions. Dimensions, 10.5 by 5.5 by 3.5 cm.; weight, 100 grams.

*Kidneys.* Left: the capsule strips off easily. The surface is free from patches of atrophy and is mottled with pale white or gray and light red areas. The cortex is swollen. It has a thickness of ten to twelve millimeters. The striæ are very coarse, and marked with pale grayish-white patches and streaks. There is a wedge-shaped opaque yellowish-white area 2 cm. in length by 1 cm. in width, which extends throughout the entire cortex; this is an old infarction. Dimensions of left kidney, 14 by 7 centimeters. Right: paler than left. The cut surface presents about the same white and red mottled appearance as the left. In this kidney also is a pale yellowish-white



wedge-shaped area 8 mm. in diameter, the remains of an infarction. There is neither hemorrhage nor hyperæmia around the infarctions, which are surrounded by a narrow pale zone.

*Adrenals*, normal.

*Liver*. It appears normal externally. The surface is smooth; free from adhesions. Dimensions, 27 by 18 by 7.5 cm. Weight, 1580 grams. Its color is reddish brown. In the substance of the right lobe, and about its middle, there is an approximately spherical area measuring 2.5 cm. in diameter. The appearance of this area is light brownish-red mottled with gray, and it is surrounded by a zone of hyperæmia. The consistence of this is about the same as the liver substance, and it apparently grows from one of the prolongations of the capsule of Glisson containing bile-ducts. Gall bladder normal.

*Stomach*. On the anterior wall about the middle are several, (8), depressed, slaty-gray or bluish-gray areas, where the mucous membrane appears thin, but here, as well as elsewhere, is freely movable on the loose submucosa. These areas may possibly be patches of simple atrophy of the gastric mucous membrane. They are irregularly oval in shape and from .5 to 1 cm. in diameter. The submucous coat, the rest of the mucous membrane, and all the remaining coats appear normal.

*Pancreas*. Firm, pale gray.

*Large Intestine*. The contents consist of soft, brownish-yellow faeces. The mucous membrane of the large intestine appears thin, especially in places; it is pale, and the follicles are not visible. In some places the mucous membrane is reddened; this is seen on the ridges especially. There is neither ulceration nor evidence of acute inflammation.

*Vermiform Appendix*. It measures 8 cm. in length, appears abnormally white and fibrous externally, and feels like a fibrous cord. Its mouth is completely obliterated, and on transverse sections, at different points, no lumen can be made out. It is impossible to pass a fine glass probe either through the mouth or into the tube on section. The diameter of the tube is 8 mm. On cross section it presents an outer smooth gray zone, probably corresponding to the original serous and muscular coats, measuring about 1 mm. in thickness. Inside of this the tissue is loose, and more opaque, gray, fibrous tissue is found.



The obliteration extends through the whole length of the tube, its free end being rounded. There are a few adhesions at this point, and in general the peritoneal coat seems thickened.

*Small Intestine.* The Peyer's patch just above the valve appears depressed, and irregularly thickened; papillary projections of mucous membrane are present in its margin. The surface of the patch presents a shaven-beard appearance. At a distance of 265 cm. above the valve is a slight or moderate constriction of the gut, produced by a new growth in the wall corresponding to the mesenteric attachment. This growth measures 2 cm. in length, parallel to the axis of the gut, and 3.5 cm. in width; it occupies a little more than one-half of the inner circumference of the gut. The growth projects only a little into the lumen; its central part is superficially ulcerated, the edges projecting and rounded. The surface of the growth has a dark bluish slaty appearance, and the same color extends into its substance to a depth of 2 to 3 mm. The consistence is firm, the color of the deeper part gray, the general appearance dense and fibrous. The growth extends a short distance into the mesentery at its attachment. 27 cm. higher up is another similar growth, smaller, measuring 2 cm. in diameter, with a depressed central superficial ulceration, and elevated, rounded, not undermined, margins. This one, also, is situated at the mesenteric attachment, and apparently the growth is chiefly in the mucous and submucous coats. The peritoneum is white, a little thickened and finely granular over the growth, but without adhesions. 130 cm. above this is a third similar growth projecting into the lumen, and situated opposite the mesenteric attachment of the gut. This growth presents, likewise, a central ulceration with elevated margins, and it projects 1 cm. into the lumen of the intestine. It measures 2 cm. in diameter. Like the others, it is of a bluish-gray color on the surface. This color extends into the substance about 2 mm. and then becomes gray. The muscular coat can be traced beneath the growth, and it appears somewhat thickened. 17 cm. above this is a thickening 1 cm. in transverse and .5 cm. in longitudinal diameter, of a projecting fold of the mucous membrane, also of bluish-gray color and firmer consistence than the rest of the mucosa. It is not ulcerated. Near it can be felt several small, rather firm nodules, in the mucous and submucous layers, the size of a hempseed. The solitary follicles of

the duodenum are a little swollen; dark, brownish-yellow bile can be squeezed through the mouth of the common bile-duct.

*Lymph Glands.* The mesenteric and retroperitoneal, portal and cervical lymph glands, in fact, all the lymph glands of the body, so far as they can be examined, are normal. There are no traces of any metastases from the intestinal tumors, except the one in the liver. The liver was thoroughly cut up and no other growth discovered.

The urinary bladder contains 20 cm. of the turbid fluid, showing under the microscope great numbers of desquamated epithelial cells and spermatozoa.

Frozen sections of the fresh kidney show an extensive infiltration with small round cells. This infiltration occurs especially in areas in which the tubes cannot be made out distinctly, as well as in lines between tubes comparatively or entirely normal. Some tubes with small, atrophied, sometimes fatty epithelium, can be seen with considerable accumulation of lymphoid cells in their neighborhood. One yellowish waxy cast was seen in a tube in the cortex. In the collecting tubes near the papillæ are some fatty epithelial cells. There is, however, little fatty degeneration of the epithelium, and a large number of cortical tubes look perfectly normal with excellent epithelium. Some glomeruli appear indistinct, others appear normal. The pale areas producing the mottling of kidneys probably correspond to accumulations of lymphoid cells.

Similar sections of the liver show extensive fatty degeneration of liver cells, and a great deal of yellow pigment, especially in the centers of the lobules.

The heart muscle is sprinkled over with very fine oil globules. Striæ distinct. The fatty change seems to be quite diffuse.

Cultures from the peritoneum, spleen, liver and bile were sterile. From the kidneys and lungs, growths of the bacillus coli communis were obtained.

#### HISTOLOGICAL EXAMINATION.

The specimens were placed at the time of the autopsy in alcohol and other hardening agents, and, as already noted, the autopsy was a very fresh one. At the autopsy three distinct tumor masses were found in the small intestine, excluding the swelling noticed in connection with the patch of Peyer just above the valve and one of the valvulæ conniventes in the uppermost portion of the small intestine. The



largest of the tumors was situated lowest in the intestine, the smallest highest. On microscopical examination no difference was found in the structure of the tumors.

*The Small Intestine.* The largest nodule will be described. As it does not differ from the others, its description will suffice for all. But as there are minor differences in the extent of the invasion of the several tunics of the intestine, the variations will be referred to later.

The tumor is composed mainly of cells of the lymphoid type not to be distinguished from the cells of the normal lymphoid tissue present in the intestine. Between the cells are bands of connective tissue of different sizes, giving an irregular, reticulated appearance to the tumor. These bands vary in thickness and in density, and the older ones are quite homogeneous, while all are poor in fibrillæ and connective tissue corpuscles.

The nodule occupies principally the mucous membrane and submucosa, although all the coats of the intestine are invaded in this situation and there has been an extension to the mesentery. The mucous membrane has been so greatly altered that its recognition is difficult. It is reduced to a mere film on the surface of the nodule and retains hardly any trace of its normal structure. But as this change is only a part of a more general process to be described later, it will not be considered here.

The greatest development of the nodule has taken place in the submucosa. The muscularis mucosæ is not present in the nodule, but it may be seen on either side, although greatly altered. The submucosa is pressed apart, and in large measure its structures have disappeared from the site of the tumor. The submucosa and the overlying mucous membrane on each side of the nodule are raised above the surface of the intestines and are folded on themselves.

The muscular coats of the intestine are involved. Although beyond the nodule they are not altered in thickness nor in their relations, yet at its margins the layer of circular fibres becomes thickened and is drawn up to accommodate itself to the new position demanded by the dragging of the tumor. As the middle zone of the nodule is reached, the circular muscular coat has become so greatly infiltrated with cells that its fibres are spread apart, more or less obscured, and many of them are broken across. The longitudinal muscle continues in company with the circular as the bending pro-

ceeds, its fibres becoming more and more indistinct, on account of the cellular invasion, until, just opposite the summit of the tumor, it is not to be distinguished any longer. The peritoneal coat is likewise infiltrated. It is thickened by this and the process has passed into the mesentery.

From the nodule just described it would be supposed that the process is circumscribed, but this is not the case. Besides the accumulation of lymphoid cells visible to the naked eye as nodules, there are wide-spread collections of similar cells throughout the intestine. These are in greatest abundance in the parts immediately adjoining the nodular formations. In these situations all the coats of the intestine are involved, but at distances, more or less great, are found isolated processes similar to the nodules, but having no connection with them. (Fig. 2, Plate v.)

In the diffuse processes the submucosa seems to be the favorite seat for the collection of the cells, just as in the nodular ones. The mucous membrane is affected, however, as well as the muscular coats.

It is possible to trace the manner in which the cells spread to the submucosa in some cases. In these the process seems to begin in the mucous membrane and to be confined to it for a period until the muscularis mucosæ is seen to give way, when the cellular invasion enters the submucosa. On the other hand, there are collections of similar cells around blood-vessels in the submucosa even greater at times than in the tissues generally. These are not directly traceable to the processes proceeding from the mucous membrane.

The muscularis mucosæ is often thickened and has evidently degenerated, even though there be no especial collection of cells in it; and again it is altered by a new growth of connective tissue. In other places the muscularis mucosæ is so completely infiltrated with cells that it is quite or totally obscured.

The diffuse process is met with again at the boundary between the circular muscle and the submucosa, and even more between the two layers of muscle themselves. It appears occasionally as if the cells had worked their way into the muscle by insinuating themselves in the connective tissue septa separating the muscle from the submucosa and one bundle of muscle fibres from another, and finally by spreading out freely between the two tunics (Fig. 3, Plate v). As a rule the diffuse process leaves the peritoneal coat uninvaded.



The patch of Peyer just above the valve was noted to be swollen and to send up papillary projections at its margins. The same condition is present in this instance as in the larger nodules, with the exception that it is not so advanced (Fig. 1, Plate v). This difference in the extent of the process in the mucous membrane and submucous coat is shared by the other tunics. The muscle is not disturbed in its course, nor the peritoneal coat much altered. This difference is again seen in the remaining smaller nodules, the invasion being chiefly confined to the mucous membrane and submucosa; although in these the subordinate layers are more involved than in the enlarged Peyer's patch.

The mucous membrane of the intestine throughout presented a most surprising and interesting condition. At the autopsy it had been noted that it was much thinner in places than is normal and appeared to be atrophied. In fact, the entire intestine, with slight exception, from the pylorus to the anus, exhibits a most extensive degeneration of its mucous membrane associated with atrophy.

The epithelial layer, that is the superficial columnar epithelium, is absent. What forms the uppermost layer of a large part of the mucosa is a material formed of an irregular granular substance containing few faintly-stained cells. Just beneath this layer is a line, varying in width and somewhat tortuous. This is not cellular, but is made up of a condensed tissue into which the villi (in the small intestine) and the glands of Lieberkühn have been converted. This tissue, corresponding to the mucosa, stains in eosin. It is made up partly of a granular substance and partly of fibres, but no particular arrangement of fibres can be made out with certainty. And yet it would seem as if the fibres were between more or less regular masses of the granular material. The fibres are quite wavy and contain a few spindle-shaped nuclei (Figs. 1 and 2, Plate v).

In the portions of the intestine to which this description refers the usual structures of the mucous membrane are not to be made out at all. The villi and crypts of Lieberkühn are completely wanting; while in another situation not far distant, something of the normal glands can be recognized. However, even here, it is the gland forms rather than the cells which are preserved, and it is in the depth of the mucous membrane near the muscularis mucosæ that a few crypts in cross section are still visible. Near the surface, too,

some are seen, but they are even more altered; they are partly filled with granules, and bundles of connective tissue separate them from one another. Nothing is left of the lymphoid tissue normally present between the glands. In these places the cells have become disorganized and converted into the granular material just spoken of. From its appearance it is probable that much fat was present in it in the fresh state. There is a new and abundant growth of connective tissue throughout these areas. It is present between the masses of granules and over and through them, and it is often very tortuous. No undue infiltration of this tissue with round cells has occurred and leucocytes are not abundant in it.

While in the main the mucous membrane shows the characters just described, other parts of the intestine exhibit the change in varying degrees. As before stated, the epithelium of the surface is completely gone, and the crypts are generally altered. Yet there are remnants of follicles in the deeper layers of the mucous membrane, in some places just above the muscularis mucosæ. As a rule, however, in such glands, the epithelium is disturbed in arrangement and partly exfoliated. It is irregular in form, even disintegrated, and young connective tissue is made out within the glands. The mucosa is thinner than is normal, and more young connective tissue cells are present than in more advanced areas.

Still other parts of the mucous membrane have been completely converted into connective tissue. These portions are extremely attenuated. No epithelial, villous or other normal structure remains; all that one finds is a layer of newly-formed, quite tortuous, not especially cellular connective tissue, lying on a much altered muscularis mucosæ. This is the most advanced stage of the cirrhotic process (Fig. 4, Plate v).

An earlier condition than we have yet described exists. Where this is found the mucosa is of normal thickness. The epithelium of the surface is, however, absent, but the general form and arrangement of the underlying structures have been better preserved. The cells of the villi (this description refers to the small intestine) and crypts are manifestly altered. The villi are wider than normal, many are depressed, and all show a certain amount of the granular contents previously described, but some of the cells remain. The crypts have hardly retained their normal shape; the cells which they



contain are devoid of nuclei; many have irregular contours, take the eosine stain deeply and their refraction is increased. They are evidently hyaline and necrotic (Fig. 3, Plate v).

In many of these glands of Lieberkühn single cells are rarely seen. More often the cells are fused together into masses of hyaline cylinders, stained in eosine, which fill the gland spaces. Between the glands a fine connective tissue is to be seen; the usual lymphoid tissue is diminished or absent. Few or no polynuclear leucocytes are met with in this tissue.

In the mucous membrane, the seat of the infiltration with round cells, in the submucosa and in the nodular aggregations, small particles are found, now in slight amount, and now in large quantity. These particles stain deeply in nuclear dyes, are irregular in size and shape, and consist of nuclear detritus. In the submucosa and in the muscle, in a few places, considerable collections of yellow blood pigment are found.

In the small intestine the nodular developments of new tissue as well as the more diffuse may be within the lymphoid structures or they may not. It is not possible, however, to demonstrate a pre-existing solitary or agminated follicle in all the nodules, and in the other form it seems to be a matter of accident. On the other hand, there are collections of lymphoid tissue (solitary follicles) that remain unaltered. The disease processes may extend nearly or quite to these, and yet they are unchanged.

The smaller nodules themselves do not differ from the largest one described, but whereas the mucous membrane over the latter is completely altered, and at best reduced to a mere film of wavy connective tissue enclosing a few remnants of crypts hardly recognizable, that over the smaller ones is much less changed. Where ulceration had occurred it affected the mucous membrane, or its residue, on the summit, and extended into the new growths themselves.

In several places in the small intestine the submucosa was very loose, permitting the folding of the mucosa upon itself. In consequence of this a peculiar appearance is obtained on microscopical sections. There are, apparently, three layers of mucous membrane with two intervening layers of submucosa before the muscle is reached. How far this may be explained by the contraction of the newly formed connective tissue dragging on the submucosa it is not possible to state.

*Vermiform Appendix.* The mucous membrane of this portion of the intestine shows the same kind of changes as the rest of the large intestine which is affected. There is a diffuse invasion with lymphoid cells, and the crypts of Lieberkühn exhibit different degrees of desquamation of epithelial cells, and some are completely degenerated. The submucosa is not infiltrated with lymphoid cells in some places, while in others there is a marked invasion of this coat, and the underlying muscular coats are also affected. Where this is marked the thickness of these coats is much increased. The peritoneal coat is thickened and contains occasional accumulations of round cells.

*The Large Intestine.* Pieces from the ascending colon, descending colon and sigmoid flexure were studied. In the first, a considerable part of the mucous membrane is quite normal, and the crypts of Lieberkühn well preserved. But in other places there are rows of crypts quite altered that run into the normal ones. The degeneration and atrophy, while of the same general character as in the small intestine, are not so extensive. The muscularis mucosæ is infiltrated with cells of the same type as in the small intestine, and the submucosa contains collections, but there are no nodular aggregations of them. The peritoneal coat is somewhat affected, but the solitary follicles are normal.

In the descending colon there is more atrophy of the mucous membrane. However, there are places in which the mucosa is normal, or nearly so, but they are fewer than in the previous part. The submucous coat is infiltrated to a considerable extent, the cells having been collected into foci. The sigmoid flexure (Fig. 1, Plate VI) is least affected. But even this has not escaped altogether. There are patches of atrophy of the mucous membrane here as elsewhere, only they are smaller and less numerous. The solitary follicles are normal.

In general, in the large intestine, the degeneration is less extensive than, and the atrophy not so complete as, in the small intestine. In both the large and small intestines no goblet cells were observed. Even where the normal structure was still preserved they were absent.

*The Stomach.* Portions containing the depressions in the mucous membrane with a small amount of the surrounding more elevated



tissue were taken, and sections made to include all the layers of the organ were examined. The surface epithelium is gone. The glandular layer is abnormal, the glands are narrow, often greatly compressed, their cellular contents indistinct and frequently degenerated. At other times the glands are not so much compressed and still contain cells, but the latter are nevertheless much altered. The intertubular connective tissue is thickened and it has overgrown the surface of the mucous membrane, thus presenting a wavy, tortuous layer.

The more elevated portions of the mucous membrane are less changed than the depressed ones, but they are far from normal. At first, in these areas and in the adjoining depressed ones, the cells in the tubular glands take a stronger eosine stain than is usual. The nuclei of the cells are visible, but the cells have greater refraction than commonly. Later these cells lose their nuclei; they become still more refractive and fill the membrana propria of the glands. Finally, single cell outlines are lost and the cells have become fused together. Even these masses do not persist, for areas are found in which all, or nearly all the glandular structures have disappeared, and for them is substituted a new growth of connective tissue.

The appearance of necrotic and hyaline cells and the development of connective tissue are unaccompanied by softening on a large scale. There are circumscribed areas in which the tissue is breaking down, and into them leucocytes have entered. As a rule, however, very few leucocytes are found in these situations. Again, in some glands, the degeneration is not of the above hyaline variety. It consists of a change of the epithelium lining them into a granular material in which, doubtless, much fat was originally present.

Hence it is evident that in the mucous membrane of the stomach, forms of degeneration and atrophy have taken place identical with those in the intestines. Here, too, as there, the increase of connective tissue proceeds hand in hand with the degeneration of the parenchymatous structures. Where these changes are slightest, no new formations of connective tissue can be seen; as they proceed this new growth becomes visible, until finally, with the disappearance of all the parenchymatous structures, the connective tissue formation is complete.

In the mucous membrane, in the muscularis mucosæ, which is itself altered, and in the submucosa, are numerous round cells. In the first two they are diffusely present, and in the submucosa, where they are in the greatest abundance, they are partly spread out and partly in collections around blood-vessels. Hence it is clear that we are dealing with processes in the stomach identical with those in the intestines, viz., the atrophy of the mucous membrane and the presence of a new formation of lymphoid cells in the tissues.

*The Liver.* The nodule in the liver is throughout a reproduction of the nodules in the intestines. It is located in several portal spaces, and it is extending into other parts of the tissues along these channels. From them it sends off projections into the hepatic lobules, and often the growth has surrounded these. It is clear that the growth has begun in a portal space and has invaded the lobules secondarily. There is a slight cirrhosis in the neighborhood of the nodule, but it does not form a capsule for the tumor. Small islands of liver tissue are cut off at times from the main body and are enclosed by the cells of the nodule, and the liver cells in these places have not always suffered degeneration.

On the other hand, at the margin of the new cells and liver tissue, degenerated liver cells are found. These are usually hyaline, and in the mass of new cells, single cells and small groups of liver cells occur which have undergone degeneration. In this case they may for a time retain their nuclei; later they become vacuolated, stain deeply in eosine, lose their nuclei and disintegrate. Fragments of nuclei are found in the liver, but only in small amount.

*The Kidneys.* In the kidneys there are numerous collections of cells of the lymphoid type. These occur in the cortex principally, but they are also found in the pyramidal portions. In the cortex they are not spread evenly over the surface, but are gathered into foci which lie between the tubes and over them, and they often surround the glomeruli. Here, as in the liver, the entrance apparently is by means of the blood-vessels.

To this disposition of the lymphoid cells was due the mottled appearance of the kidneys. There are, indeed, such enormous numbers of these cells present that the swelling of the cortex may in this way be accounted for. In the pyramidal portion of the organ there are, as mentioned above, fewer collections of lymphoid cells and they



are not so widely distributed. These cells are not to be distinguished from the cells of the nodules and diffuse growth in the intestine, the diffuse cellular process in the stomach, and the nodular one in the liver.

Aside from the obliteration of tubules by the growth in the kidney, there are evidences of degeneration in the kidney of the epithelial cells of the tubules. It is true that much of the epithelium is well preserved, but now and then masses of degenerated epithelium are encountered. The change is principally of the hyaline variety, although limited fatty changes have taken place, as shown in the fresh section. A few glomeruli show a fibroid thickening, and some are entirely obliterated. However, it is probable that the atrophy in this instance is independent of the process we are describing.

*Lymphatic Glands.* There was no involvement of the mesenteric glands, the colic glands and the gastro-hepatic glands, neither were the superficial or other deep glands affected in any way by the disease process.

#### RELATION AND NATURE OF THE LESIONS.

When we endeavor to bring these various organs under a common head, in so far as their pathological changes are concerned, we are struck with a certain succession of phenomena which they present. All the affected organs exhibit parenchymatous changes, although not in equal intensity. At times they are of a mild character, at times of the most profound. This difference is seen not only on comparing one organ with another, but in the same organ in different situations and at different stages of the process. Following these degenerations, we have in this case, as probably in all others, a new growth of connective tissue replacing, as it disappears, the degenerated parenchyma.

Then there is another process in operation. This we have already described in the nodular and diffuse formation of lymphoid tissue in all the affected organs.

It becomes necessary to examine the possibility of the relation of the two sets of processes, as they occur in the same organs, where they are closely interwoven; and to consider the pathological processes to which they belong.

The character of the new formations of tissue suggests at once, from a histological point of view, that of the infectious granulomata. The dissemination of the process, the involvement of several organs, and the clinical course of the disease favor such a view, while the degenerations associated with the new growth are a strong warrant for such an assumption. Admitting the possible truth of such a conception, to which of the described granulomata does such a process properly belong? Manifestly tuberculosis can be immediately excluded, for the new formations have neither the histological structure of tubercle, nor are the reorganized forms of degeneration to be found. Syphilis is not to be considered for similar reasons. So far as more acute processes, such as typhoid fever, are concerned, such great differences exist in the macroscopic and microscopic appearances in the two cases that the possibility can likewise be safely rejected. But if the process which we have described cannot be reconciled with any of the granulomata mentioned, because in its structure and in its fate it differs materially from them, yet it must be admitted as exhibiting certain features in common with them.

We have in this case the production of tissue of the granulomatous type appearing first, doubtless, in the intestine. It is found there forming partly circumscribed nodules and also spreading out diffusely. The same tissue is found elsewhere in the body, as in the stomach and kidneys, where the diffuse variety is met with, and in the liver where the nodular form is seen.

In the intestine the process is extensive. The small intestine is the primary seat of the disease. The oldest and largest nodule occupied the lower part of the small intestine; the youngest and smallest nodule was highest up, while a nodule intermediate in size and probably in duration lay between these two. The remainder of the intestine, above, below and between the nodules, was more or less affected by the diffuse process. The diffuse growth is not everywhere continuous with the nodules, nor does it form an unbroken and uniform layer. A part only of the diffuse process arises from the spreading of the nodules, while areas of intestine are found in which neither form of the growth is present.

When these facts are considered it can hardly be maintained that the process in the intestine is due to an implantation from above and direct extension from the nodules, for the oldest tumor is lowest and



there is not a continuous line of growth. Again, in the stomach the process is less extensive than in the intestine, yet less of this organ was saved than could have been desired, and it is not improbable that the alterations here were more general than was at first suspected. If, then, the presence and extension of the process in the stomach and intestine did not occur in either of the ways mentioned, it is necessary to consider by what other means they might have taken place. It is not likely that in these situations the occurrence was through the circulation, even though this means should not, perhaps, be totally excluded. It would appear more probable to suppose a morbid agent, which had entered the alimentary canal from without, as having acted directly in producing them. In the case of the liver and kidneys, however, there can be little doubt that the mode of infection was by means of the circulation.

Directing our attention, now, to the degenerations not in the new growths themselves so much as in the tissue in which they occur, we are impressed with their severity and extent. It is sufficient for our present purpose to consider this in relation to the intestines and stomach.

From our description, these degenerations are seen to be of the most intense character. The structures of the mucous membrane in these organs have been largely destroyed and obliterated, and from the different stages met with, especially in the intestine, it is evident that the process has been of a progressive nature. In this way we are enabled to understand the degrees of it, and to interpret properly the affection of the stomach, liver and kidneys, for in these organs it is of more recent origin. Hence we are dealing with a growth which, while not undergoing marked degeneration itself, is associated with the most pronounced alterations in the tissues in its immediate vicinity and at a distance. And it is probable that the new growths themselves may, after a time, be the seat of further changes. This is shown in the ulcerations found in the nodules and in certain small areas of mucoid, or an allied change found in connection with the largest nodule.

This series of changes, the multiple nature of the process, its histological structure, its distribution in various organs, the degenerations which it occasions and even undergoes, are suggestive, to say the least, of that form of disease process which we term the infective granulomata.

In order that the process may be fully understood as we conceive it, it is necessary to dwell for a moment on the manner in which the tissue changes may be produced. In the case of those tissues directly affected by the new growths, especially those in which the nodules have formed, it might be supposed that the necrosis of tissue was brought about by anæmia of the parts. But if this were thought sufficient in the case of the nodules, it could not hold for the diffuse formations; moreover, it could not be considered in connection with those parts in which no new growth has taken place. But it is not necessary to admit such an explanation for the nodular areas, when it is recalled that in those affections in which there is simple enlargement of the lymphoid follicles of the intestine, or when, as in simple lymphomata, large nodules are present in the intestine, no such necrosis of the tissues is induced. And, finally, the form of necrosis is not that of simple anæmia.

On the other hand, in such diseases as bring another element to act, even slight enlargement of the follicles, or slight development of the disease process in the tissues, may give rise to necrosis of tissue. This is true, for example, in typhoid fever and tuberculosis. In these diseases it is not the new growth which causes the necrosis, but an agent which is the product of the specific cause of the disease in each case.

We are led, therefore, in considering our case, to the conclusion that we are dealing with a process not unlike in its history the infective granulomata. This view is not based upon one peculiarity, but follows from a number of characteristics distinctive of this class of diseases.

As it is now conceived that the peculiar toxic substance acting on the tissues in tuberculosis causes caseation, in syphilis a slightly different form of necrosis, and in typhoid fever one still different, so it may be assumed that in this instance we are dealing with a toxic substance capable of causing profound degenerative changes in certain tissue elements in the body. Nor is it necessary for the degenerative changes to be produced only at the seat of the new formation of infective tissue, for by a diffusion of the poison in contiguous parts similar effects may be had, even when the new tissue is not present.

We are brought, then, to the conclusion that the process is an infective one and, so far as our observation has gone, it is of a pecu-



liar nature. Whether we shall find a clinical picture peculiar to such cases is doubtful, and whether the pathological process, as here described, is entirely distinct our present inquiry does not permit us to say. Yet when the case is considered in all its relations, the suggestion of the operation of a specific cause is too strong to be neglected.

Whatever the cause in question may be, it is evident that it must be regarded as of an infectious character. Of the nature of this agent we speak with the greatest reluctance. Without pretending to have satisfied ourselves of the significance of the bodies about to be described, we must state that they are foreign to the tissues in which they are found, and are not to be regarded as altered cells or fragments of nuclei in the usual sense.

These bodies are round, oval, or slightly irregular in shape, and they consist of a rim of protoplasm that stains faintly in eosine, and each one contains a particle that stains in hæmatoxylin. The stained particles in the interior of the protoplasmic rim also show variations in form. They are round, oval or crescentic, and they occupy either the center of the protoplasmic body or have an excentric position. Sometimes two particles are found surrounded by protoplasm and forming the body. These bodies are not contained, so far as our observation has gone, within other cells. They are not pigmented, and, while they vary in size, they are much smaller than the tissue cells among which they are found, and do not exceed one-third to one-half the size of a red blood corpuscle.

They are distributed irregularly in the diseased areas in the tissues, and an occasional body may be seen in parts adjacent to the affected areas. They have been found in the stomach, intestines, liver and kidneys. They are most readily seen, perhaps, and their forms best studied in the kidneys, where they occur in some number, especially among the lymphoid cells in the older affected areas, in which the tissues are most altered.

As to the intimate nature of these bodies, we have very little to communicate. They are manifestly not bacteria, and if they are organisms at all they must be held to belong to the animal parasites—perhaps the protozoa. However, the possibility that they are not parasites, and play no causative rôle whatever in the disease, is not excluded.

There is an affection which the process we have described may be held to resemble. This is lympho-sarcoma.

In many respects the latter disease conducts itself like an infectious malady, and its similarity to the infective granulomata has been suggested more than once. Klebs<sup>1,2</sup> first pointed out on anatomical grounds the likeness of these processes, and he regards the lympho-sarcomata as exhibiting great malignancy from the beginning, including them in the groups of leucocytoma, to which he referred tuberculosis, syphilis, glanders, and typhoid fever. He dwells on their unusual malignancy in some cases, the infection of other glands and distant organs, and states that in other instances they may become smaller spontaneously or under the influence of medication. Cohnheim,<sup>3</sup> likewise, urges in a very convincing manner, such a classification on anatomical grounds, and he speaks in addition of the tendency to ordinary inflammatory changes in the neighborhood of the affected glands, a point of resemblance to other infectious processes; again, Virchow<sup>5</sup> speaks of its metastases as being less like an independent process, as in cancer, than like an inflammatory affection which gradually invades the surrounding tissues. He further compares the lympho-sarcomatous process first to scrofula and then to tuberculosis, according as the affection is localized in the lymph glands or gives rise to metastases. However, from these it is distinguished by the absence of the caseous metamorphosis; fatty degeneration may occur, but it does not reach a high degree. The amyloid change he has found only once, and ulceration is considered by him as rarely occurring.

The observations of Wagner<sup>7</sup> on the peculiar disease affecting the cobalt miners of Schneeberg are of the greatest interest in this connection. Before the study of this affection by him it was generally believed to be cancer. It would seem as if all persons working in these mines for a number of years become affected with a disease of the lungs characterized by the formation of nodules, which grow slowly and often reach a considerable size. From the lungs the pleura and lymphatic glands become affected, and finally metastases occur in the liver and spleen, and death results from a gradually increasing marasmus. It is pointed out that other people who live in Schneeberg, but do not work in the mines, are free from the disease, and that in other localities, southern Sweden, for instance,



where the same metals are mined as in Schneeberg, the disease is unknown. Wagner proved this affection to be lympho-sarcoma, and Cohnheim<sup>3</sup> asks if it is not probable that the disease owes its origin to an entirely different sort of poison, one of an organized nature, contained perhaps in the water drunk in the mines.

Recently Dreschfeld<sup>9</sup> has emphasized anew the probable infectious nature of lympho-sarcoma, and finds in the histological structure of the tumors, their mode of spreading, and, in the acute cases, the occurrence of fever and ecchymoses, strong presumptive evidence.

It must be admitted that there are features in our case which agree well with the description of lympho-sarcoma as given by these authors. Yet there is in it something more. No author whom we have consulted alludes to the occurrence of tissue degenerations secondary to the lympho-sarcomatous process, as being a part of the disease. A number of writers describe tissue changes in the affected organ, as we shall see, but they are usually of small amount and their importance is not considered.

#### CASE 2.

Since the study of the preceding case has been completed we have secured material from another case. Unfortunately, the history which we are able to give of this one is very brief. Moreover, the nature of the lesions which we shall describe was not suspected during life, and not wholly appreciated at the autopsy. In consequence of this, less of the tissues was saved than would otherwise have been done; yet, we are able from the material at hand to add to the first case important substantiation.

The autopsy was made outside of the Hospital on a patient of Dr. R. W. Johnson by Dr. Councilman, to whom I am indebted for such particulars of the case as I possess, for the tissues and the examination of the fresh material.

The tissues were derived from a girl eleven years of age, who lived in an asylum for poor children. Up to the day of her death the child had been regarded as well, and on that day, the weather being very warm, she took a cold bath an hour or so after breakfast. Soon after the bath she became drowsy, sank into a comatose condition, and died at 4 P. M. of the same day.

The autopsy was made very soon after death. The child was noted to be well nourished, and not anæmic, and presented, in general, a picture of having been in vigorous health prior to the sudden onset of the symptoms which proved rapidly fatal. A large hemorrhage had taken place into the right side of the cerebrum, opening into the lateral ventricle. There were no other discoverable lesions in the body, excepting those in the alimentary canal about to be described.

Beginning with the pharynx and extending throughout the alimentary canal, the lymphatic tissues were markedly hypertrophied. The swelling was well marked in the stomach and intestines, and it was not limited to the lymphoid follicles. The mucous membrane of the intestines presented elevations and depressions, and the interspaces between the swellings were so slight in some places that the elevated patches were actually in contact. Yet, as the central parts were more swollen in these instances than the peripheral, a wavy appearance was still evident. As a whole, owing to the new growth of lymphatic tissue within it, the mucous membrane appeared thickened and no ulceration was present. This thickening of the mucous membrane was, however, apparent only, as we shall see, and in point of fact the mucous membrane proper was thinner than is normal. Notwithstanding this increase in the lymphatic tissue in the intestines the mesenteric glands were unaffected, and the spleen likewise. The other lymphatic glands of the body were not altered so far as was visible, and there were no lymphoid deposits perceptible in the liver, kidneys and lungs.

The blood-vessels of the brain were teased out in the fresh state and examined in physiological salt solution. No fatty degeneration nor other abnormal condition could be detected in their walls. The blood was examined and no increase of white corpuscles found.

The microscopical examination of the tissues, which were placed in strong alcohol at once after the autopsy, embraced the intestine, the duodenum, jejunum and ileum, and the liver and brain. We regret that pieces of the stomach, kidneys and other organs were not saved. However, it would seem as if the main interest of the case lay in the condition of the intestine, and this we were fortunately enabled to study.

The irregularity of the free surface of the intestine and the thickening apparent to the naked eye are observed upon microscopical sec-



tions to be due to the development, partly within the mucous membrane and partly in the submucosa, of nodules of lymphatic tissue, varying in size, and sometimes confluent. Although these nodules have a general similarity of structure, and consist principally of lymphoid cells, yet there are many cells of an endotheliod type present in the centers of the nodules. The framework of the nodules is usually delicate, but an occasional thicker band of connective tissue is observed. Blood-vessels are also found in them. The largest nodules on the hardened sections did not exceed a hemp-seed in size, the smallest were hardly larger than miliary tubercles. The latter were sometimes entirely confined to the mucous membrane, while the former occupied the submucosa as well as the mucous membrane.

*The Duodenum.* The smallest nodules are observed to lie entirely in the mucous membrane. These sometimes impinge on the muscularis mucosæ, but this structure is as a rule not penetrated. In a few instances small offshoots from the small nodules extend through the muscularis and enter the submucosa. The larger nodules extend deeply into the submucosa, and in such cases the muscularis mucosæ is lost in the nodules, to be seen again on each side. There is only a slight tendency for the newly developed lymphatic tissue to become diffused through the various coats of the intestine and to spread from the nodules. The spreading is seen along the septa between Brunner's glands, and the lymphatic vessels in the submucosa sometimes contain numbers of lymphoid cells. The latter condition may occur even when the submucosa itself is quite free from infiltration. The muscular coats do not participate in the process.

The mucous membrane proper is observed to be much thinner than is normal. Not only is this true of the mucous membrane taken as a whole, but some portions are thinner than others. At first glance it is evident that the number of stained nuclei in the mucous membrane is much diminished, and it is next perceived that certain structures have suffered more than others.

The columnar epithelium is nowhere present. The villi are much reduced in actual number, and, indeed, in some places very few remain distinguishable by their villous form. Even these few are altered. They are thin and threadlike, their walls are indistinct, and their contents consist of cells without nuclei and fragments of cells having a granular appearance. The whole stains in eosine, with

hardly a nucleus which stains in hæmatoxylin. Beneath these structures comes a tissue containing crypts of Lieberkühn. The alterations in this layer are marked, but not everywhere the same. In the places more nearly approaching the normal the glands are tolerably well preserved, but they are short, and overlying them is a tissue imperfectly reticulated, containing granules. This uppermost layer, excluding the villi spoken of above, seems to have arisen from villi which have become converted into this structure. With some exceptions the crypts are not so well preserved on the surface as they are in the depth of the mucous membrane.

The degeneration of the crypts of Lieberkühn takes place in two principal ways. According to one there is a desquamation of the epithelial cells lining the crypts, and the lumina may become quite filled with cast-off cells. Many of these cells are smaller than normal ones, and while some possess nuclei which stain readily, others have lost their nuclei, and still others have suffered a more or less complete mucoid metamorphosis, as shown by the characteristic staining with hæmatoxylin. In such a degenerated gland a few leucocytes may be seen, but the number is inconsiderable. The final step of the process of destruction consists in a more complete breaking up of all the cells, so that only fragments and filaments are left, and empty and collapsed glands are to be seen.

The other mode consists of a change similar to that described in the previous case, in which a hyaline form of necrosis of the gland cells was observed. This form is found more abundantly in other parts of the intestine and will be referred to again.

The glands of Brunner suffer also. Those nearest the surface are more affected than the deeper-lying ones, and sometimes a single acinus only of a group has undergone degeneration, while again, several acini in close proximity are affected. The mode of their degeneration accords with the first one mentioned above.

The mucous membrane is most altered over the seat of the largest nodules. In such situations it is so greatly changed as to be quite unrecognizable. It consists of an attenuated layer of granular and slightly reticulated structure, staining in eosine, scarcely or not at all in hæmatoxylin, devoid of crypts and denuded of villi. The best preserved mucous membrane is found in the interspaces between nodules, but we can say that so far as the examination of numerous



sections, from different parts of the duodenum, permits one to infer, there was no normal mucous membrane present.

*The Jejunum and Ileum.* The nodules in these portions of the intestine are similar in structure to those in the duodenum. They are found here, as there, in the mucous membrane alone, and in both the mucous membrane and submucosa. Again, the larger nodules are either single or confluent; but the confluent type is found here oftener than the single nodules. The mucous membrane over the nodules behaves very much as in the duodenum. The attenuation of it is greater, however, over the largest nodules in this situation than over those in the duodenum, and the uppermost layer of the nodule itself is in some instances degenerated, and considerable nuclear detritus is to be found. The crypts show especially the hyaline form of necrosis, although their cells, which are the structures especially affected in this way, are not so highly refractive as in the previous case. Villi are more abundant in sections of the jejunum and ileum than in the duodenum, but they are altered, although the degree of change is not so advanced as in the latter situation. In some of the lymph channels of the submucosa, lymphoid cells are found, often in considerable number.

*Liver.* In the liver there are small collections of lymphoid cells, irregularly placed in the lobules, and probably originating from the intestinal affection. These nodules are quite small, sometimes not larger than the area of a half-dozen liver cells, and then they may attain the size of a miliary tubercle. They are irregular in shape, and appear as round, oval, or even more elongated areas.

*Brain.* Very little could be made out of this tissue excepting the hemorrhage. The source of the hemorrhage was not discovered.

We would draw attention to the fact that the bodies which we described as peculiar in the first case have been found again in this one. They are, if anything, more numerous in this than in the previous case, and the description given there suffices equally for those present here. They occur in the intestinal nodules and in the areas in the liver, but they are more numerous in the former situation.

Comparing the two cases which we have described, they are seen to possess much in common. Unfortunately, the analogy is less complete than it might have been had more tissues from the second case

been preserved. But the intestinal lesions in the two instances resemble each other so greatly that, for the present, the other features may be overlooked. In both we have to deal with a process, one of the chief effects of which is to give rise to a new formation of a granu-lomatous tissue, occurring as discrete nodules and as a diffuse formation. The location of the new growth of tissue is likewise similar, and its tendency to be associated with distinct and well-marked degenerations in and atrophy of the mucous membrane is to be remarked. Moreover, in each, in the diseased areas, certain peculiar bodies occur which, while not at present to be held as causative, are foreign to the tissues and are not to be excluded from playing a part in the disease process.

Notwithstanding such extensive disease of the intestinal tract, the mesenteric glands and spleen escaped in both cases. But whereas in the first the degenerations in the alimentary tract were associated with an abundant new growth of connective tissue in the affected parts, no such condition was present in the other.

However, in considering the two cases in the light in which they have been presented, it may be well to take into account that the one occurred in an adult who presented a train of symptoms extending over a period of at least several months; the other in a child who, strange to say, suffered no perceptible ill effects from the extensively diseased condition of her alimentary tract, but who died suddenly from a lesion not clearly to be reconciled with the other conditions found at the autopsy. What further changes might have taken place in the degenerated areas in the intestine, but for her sudden death, can only be conjectured.

#### REVIEW OF THE LITERATURE.

Much has been written on the affection known as lympho-sarcoma, and the literature of the subject is to be sought under a score of names which have been proposed for it at different times and in different places. The disease was first described by Hodgkin<sup>11</sup> in 1832; afterwards it was called by Wilks, Hodgkin's Disease, Anæmia-lymphatica; by Cohnheim, Pseudo-leukæmia; by Trousseau, Adénie; by Ranvier, Lymph-adenia; by Musick, Lymphatic Cachexia. With reference to the pathological changes which it



induces in the various organs, it has been called Vascular sarcoma of the lymphatic glands, Craigie; Malignant lymphoma, Billroth; Lympho-sarcoma, Virchow; Malignant lympho-sarcoma, Langhans; Lymph-adenoma, Wunderlich, Ranvier; Desmoid carcinoma, Schulz. It is needless to say that much confusion is necessarily introduced into the study of the disease by the abundance of designations which it possesses. At the present time, however, many of them have fallen into disuse, and in this country and Germany the affection is for the most part described under the titles lympho-sarcoma, malignant lymphoma, and pseudo-leukæmia, to which in England is to be added lymph-adenoma.

Weishaupt<sup>12</sup> has just discussed the applicability of some of these names, and concludes that the appellation "lympho-sarcoma" should be abolished altogether, as it serves only to bring confusion into the subject, and he proposes the adoption of the term pseudo-leukæmia, in preference to others now in use. This view, while according with ours in so far as it discards the idea of an actual tumor process characterizing the disease, assumes, nevertheless, an actual acquaintance with it which it is needless to say we do not, now possess. Until such a time as the etiology of this affection shall become known, it will hardly be possible to confine its description to any one of its names.

The literature, as indicated above, is very extensive. Without pretending to have gone over the entire field, we have made a general survey, and it is possible from this to throw together in an orderly way many cases now more or less separated, and to exclude, perhaps, others not actually belonging to the disease. Again, in very recent times, certain peculiarities of the affection have led some observers to designate as a new disease the acute form of this one, while the association of lympho-sarcoma with other affections, mainly tuberculosis, has led a few writers to the conclusion that all cases are of tuberculous origin.

It has not been our purpose, however, to gather together in this brief review every case of the disease that has been examined by us. Rather it is our intention to present those cases which bear on the one we have reported, and such others as may be considered as aiding, in a manner, a better understanding of the disease.

We have already referred to the acuteness of the course of the disease in some instances, and recently Ebstein<sup>13</sup> has described, under the title "*Das chronische Rückfallsieber, eine neue Infektionskrankheit*," what he regards as a previously undescribed acute infectious disease. His cases have been reviewed by Pel,<sup>14</sup> and compared with similar cases which he observed and which came to autopsy, and Pel shows conclusively that the cases of Ebstein are to be regarded as acute forms of pseudo-leukæmia. Renvers<sup>15</sup> reports another case associated with recurrent elevations of temperature, in which the glands principally affected were the mesenteric and retroperitoneal; metastases were present in the liver and spleen. In a case recorded by Dreschfeld<sup>10</sup> there was a large mediastinal tumor with infection of the retroperitoneal and mesenteric glands, liver and kidneys, in which the disease ran its course with elevation of temperature; but the blood contained an excess of white cells.

In this case the author found in the kidney numerous small, thick bacilli. No cultures were made, nor is it stated whether there were lesions in the intestinal mucous membrane or not. Bacilli were cultivated from the kidneys in our case; they were identified with the colon bacillus, however, and their presence there was not regarded as of any significance; for, as Professor Welch<sup>16</sup> has pointed out, the colon bacilli wander regularly when there is a lesion of the intestinal mucous membrane, and they are found almost uniformly in the kidney in such cases.

Many more cases are reported in which irregular elevations of temperature attended the disease or occurred a short time before death. But as these cases led to no misunderstanding, nor offer anything especial on their own account, and a number of them bear more directly on another part of the paper, they will be passed over now.

That there are included under this disease, affections which depend for their origin on totally different causes, and which have little more in common than the enlargement of one or more sets of glands, is quite sure. And, moreover, it would appear as if in the course of certain cases of lympho-sarcoma, a secondary process can be added to it, this one being of an infectious nature. Such would seem to be the explanation of those cases in which the pyogenic cocci were isolated from the diseased glands.



The case of Weishaupt, the autopsy having been made by Baumgarten, shows that in some instances tuberculosis of the lymph glands can simulate this affection so closely as to be indistinguishable from it by the macroscopical appearances alone. In this case there was enlargement of the lymph glands of the neck, with implication of most of the glands of the body. There were nodules in the kidney, liver, spleen and lungs. The macroscopical appearances of the glands, and the nodules in the other organs, led to a diagnosis of "pseudo-leukæmia." The clinical picture, too, was in accord with the post-mortem diagnosis. However, the microscopical examination of the affected glands exhibited areas of coagulation necrosis, and in them tubercle bacilli were found. The minute nodules in the lungs, liver and kidneys did not resemble tubercles so much as lymphomata; yet in one place in the kidney, a hyaline change was found in a nodule similar to those found in the lymphatic glands, but no bacilli could be detected. Weishaupt then examined the lymphatic glands from twelve other cases of pseudo-leukæmia, including hard and soft forms, without finding tubercle bacilli. His conclusion is that in its etiology pseudo-leukæmia is independent of tuberculosis.

Other cases in which tuberculous affections of the glands are said to have simulated pseudo-leukæmia are reported by Wätzoldt,<sup>19</sup> Brentano and Tangl, Delaunay,<sup>21</sup> Cossy<sup>2</sup> and Crocq.<sup>23</sup> In the case of the second-named writers, there were old and healed lesions in the lungs, tuberculous ulcers in the intestine and peritoneal tuberculosis, while the glands showed no caseation, but upon inoculation into guinea-pigs gave rise to tuberculosis. In a case by Claus<sup>77</sup> there were tubercles in the lungs, and tubercle bacilli in the sputa. In the kidneys, liver, spleen and lungs, even, lymphomatous nodules were present, which the author regards as distinct from tubercles and readily distinguishable from them. Another case in which both affections occurred is that of Liebmann,<sup>22</sup> but neither of these can be said to be conclusive.

On the other hand, cases of pseudo-leukæmia have been described with which the pus organisms have been associated. Mafucci<sup>24</sup> found chain-cocci in a case of malignant lymphoma, in the diseased areas only, and succeeded in cultivating them, while Roux and Lannois<sup>25</sup> isolated the staphylococcus pyogenes aureus from another case. We do not consider that there existed any relation of cause and effect in

either of these instances. In our opinion they merely represent an infection with the pus organisms added to the pre-existing glandular affection. A case is reported by Kelch and Vaillard<sup>26</sup> in which several subcutaneous tumors existed over the body, without glandular enlargement. Although the author regarded it as a case of lympho-sarcoma, there is no good reason to suppose it was one, and the histological description of the tumors corresponds quite as well with fibro-sarcoma. The only interesting point in this case is the isolation of bacilli from the blood during life and the cultivation of the organisms. In addition to the tumors there was leucocytosis, and the liver and spleen were enlarged. A case reported by Taylor<sup>27</sup> as "sloughing lympho-sarcoma of the back and other lesions of the skin and internal organs" was probably syphilitic in origin.

There are certain cases of lympho-sarcoma of quite undoubted nature in which the glandular enlargement diminished under treatment. Not a few of such are recorded. The improvement has followed the use of arsenic, given internally, and applied directly to the diseased glands by parenchymatous injection. Examples of improvement are reported by Israel,<sup>28</sup> Köbner,<sup>30</sup> Strümpell,<sup>31</sup> Billroth,<sup>32</sup> Winiwater<sup>33</sup> and others. In a case of Arning's<sup>18</sup> in which there were tumors in the skin, mucous membranes and muscles, one of the tumors was extirpated and its character determined by microscopical examination; improvement occurred in this case also. Wunderlich cites two cases, in which syphilis could be excluded, which improved under the administration of iodide of potassium.

The occurrence of ulceration and other forms of degeneration in the tissues in which the tumors developed and in the tumors themselves is not so very uncommon. It is probable, indeed, that the tendency to the graver forms of degenerative changes is not so marked in this as in some other affections, and the more minute and less evident forms have, perhaps, not received the attention which they would seem to deserve. Virchow<sup>6</sup> has again called attention to the persistence of lympho-sarcoma, and he regards them as belonging essentially to those tumors which do not ulcerate or do so only under special conditions. He says, "What is especially characteristic of them, and in consequence of which they have few parallels among tumors, is the persistence of their elements, as if they were normal elements and structures of the body. Lympho-sarcoma

does not become caseous; does not suppurate, does not tend to ulcerate; but forms nodules of a lasting nature." This utterance was made in the course of a discussion on tumors of the mediastinum. However, there are a number of undoubted cases of ulceration recorded, although the proportion is not large. It would appear that it is in particular situations that ulcerations are chiefly found. The most usual is the alimentary canal, and in particular the intestinal tract; next to this in the skin.

Coupland<sup>85</sup> reports a case of general glandular enlargement in a young woman of 25. The stomach gave evidences of post-mortem decomposition at the fundus; at the pylorus the mucous membrane was thickened, opaque and mammillated; a number of the mammillations showed central pits or depressions. These he regarded as the enlarged and ulcerated solitary follicles. The mucous membrane of the duodenum was of a dead-white color; it was infiltrated uniformly with an opaque white material, and was marked here and there with small erosions and superficial ulcerations. The ileum showed a more pronounced degree of the same process, the patches of Peyer were especially affected, and the generally smooth surface of the mucous membrane was interrupted by a ragged, villous-looking ulceration that had taken place along the margins of the valvulæ conniventes and in the site of a Peyer's patch.

The new tissue was deposited in the mucosa and submucosa. The growth of it between the crypts of Lieberkühn had caused them to shrivel and atrophy. The muscular coat was infiltrated, and the amyloid changes were present in the intestines and mesenteric glands.

In a case of Jarde<sup>87</sup> there was perforation of an enlarged and ulcerated plaque in the ileum. In most of the ileum the patches of Peyer were hypertrophied, a few only had ulcerated. In the jejunum the ulcers affected the valvulæ conniventes at times; several ulcers occurred in the duodenum, one just below the pylorus. The intestines were adherent to one another, and over the ulcerated areas there was a thick infiltration of the peritoneal and other coats, the enlarged and ulcerated plaques projecting into the lumen of the intestine from 1 to 3 cm. The mesenteric glands were affected. There were no metastases in other organs.

A case reported by Pitt<sup>88</sup> is that of a man 48 years old. In the stomach were large masses of lymphoid overgrowth, situated on the



mucous wall, forming sessile tumors. At the cardiac end, two inches from the diaphragm, were large masses, both sessile and polypoid. The growths were creamy white, soft and succulent, and the largest ones were breaking down at their bases. Large numbers of growths were present in the intestines, beginning in the duodenum and extending to the colon, which was free; many of these had ulcerated and were bile-stained. The mesenteric glands, lumbar glands, and spleen were enlarged; the peritoneum healthy.

Another is that of Pick.<sup>39</sup> At its margin between the jejunum and ileum was a mass of infiltration 15 cm. in length; this growth had thickened the mesentery to the extent of 3 cm. For a space of 4 cm. square the mass was necrotic and ulcerated; beyond this one was another but more superficial ulceration. The mesenteric and retroperitoneal glands were infiltrated. There were metastases in the liver and kidneys.

In the case of Henoch<sup>40</sup> a ring of tumor mass surrounded the intestine, and in the mucous membrane corresponding with the ring was a loss of substance about the size of a dollar. The small curvature of the stomach was infiltrated with the tumor, and the mesentery throughout. Metastases were present in the peritoneum, diaphragm, kidneys, liver, gastro-hepatic glands, retroperitoneal glands and mediastinal glands.

Still other cases are reported by Moore,<sup>42</sup> Steiner,<sup>43</sup> Legg<sup>44</sup> and others; and for the occurrence of similar ulcerations in the stomach the reports of Hérard,<sup>45</sup> Kutzner,<sup>46</sup> Wunderlich,<sup>34</sup> Hadden,<sup>47</sup> and Kredel<sup>48</sup> are to be referred to. In the description of the affection given by other authors, moreover, the occurrence of ulceration in the stomach and intestines is freely stated, for instance, by Birch-Hirschfeld,<sup>49</sup> Gowers,<sup>50</sup> Cornil and Ranvier,<sup>51</sup> Ziegler.<sup>52</sup>

Other forms of degeneration in lympho-sarcoma are hardly mentioned by writers on the subject, and the production of marked changes in the surrounding tissues has not been seen to any extent, if we exclude the direct effect of the growing tumor masses on the tissues of the part in which they are found. However, the case of Coupland, already quoted, might be regarded as an instance of degeneration in excess of the purely mechanical effect, and in those reported by Ribbert<sup>53</sup> there was atrophy of the tissues of the bronchi, notwithstanding a moderate lympho-sarcomatous development within

them. But of special interest in the cases of Ribbert is the occurrence of actual hepatization around the aggregated lymphomatous nodules in the lung. These lymphomata could be distinguished from tubercles by their appearance, and the difference was confirmed by the histological and bacteriological examinations. The character of the exudate about the nodules was unlike that of croupous pneumonia as well as caseous pneumonia, and consisted largely of epithelial cells, a varying number of lymphoid cells and fibrin. No micro-organisms were detected in the tissues nor could any be cultivated. Similar lymphoid nodules were present in other organs and parts.

Schulz<sup>54</sup> reports several cases in which, in the neighborhood of the new growth in the liver, stomach, intestines and kidneys, the epithelium of the parts was swollen, very granular, often fatty and disintegrated.

So far as the disease in general is concerned, the number of cases published is exceedingly large. Many of these have much in common and hardly demand separate consideration; some have interest, perhaps, from the number, size or situation of the metastases, while others may be valuable to us on account of their resemblance in one or more particulars to our case, or because they happen to illustrate a special feature of the disease process. We shall not attempt an abstract of every case in our possession; we hope to give a few which are interesting and instructive, and refer to the bibliography hereto appended for a more complete list.

Murchison<sup>55</sup> reports a case of a large tumor in front of the spine which was covered by the intestines. The tumor consisted of the enlarged mesenteric glands together with an enormous thickening of the coats of the duodenum and upper parts of the jejunum. The thickening was due to a deposit of new tissue in the subserous and submucous tissues. The mucous membrane of the intestine was not ulcerated, nor were the follicles enlarged. Similar deposits occurred in the peritoneum, diaphragm, fundus of urinary bladder, in the liver, kidneys and heart muscle. The new growths consisted of lymphoid cells, and were distributed along the course of the portal canals in the liver, and occupied the interstitial tissues of the kidneys overlapping the tubules. A second case of Murchison's<sup>56</sup> had general glandular enlargement with metastases in the spleen, liver,

diaphragm, lungs and dura-mater. The kidneys and intestines were unaffected. The histological examination of this case by Dr. Sanderson showed that the new growth in the liver originated in the portal spaces.

In a case published by Suckling<sup>57</sup> there were multiple growths from the dura-mater, and the intestinal glandular apparatus was affected. Moreover, there were enlargements of the mesenteric glands and liver, and the left kidney contained a nodule. Wiegandt<sup>58</sup> reports a case with nodules in the heart muscle, and general affection. In the kidneys the nodular growths were not so sharply circumscribed as they appeared to be on naked eye examination.

Cohnheim<sup>4</sup> has described an interesting case. The cervical submaxillary, retroperitoneal and inguinal lymph-glands were enlarged. The spleen was enlarged. The left kidney likewise, and the whole surface was mottled with wide, often confluent, blood-red spots and lines, the ground substance being white. The hemorrhages were mostly superficial, so that the parenchyma itself exhibits a variegated appearance, the white exceeding the red patches. The right kidney was similarly but not so extensively affected as the left. The intestines were normal. The liver was large, the acini were surrounded with remarkable regularity by a translucent ring of light gray color one-half cm. in thickness. These were made up of collections of lymphoid cells occupying the portal spaces and sending offshoots into the acini between the rows of liver cells. In the kidneys the greatest accumulation of cells was in the intertubular tissues.

In the case of Eberth<sup>58</sup> there was slight enlargement of the mesenteric glands; the mucous membrane of the stomach contained a large number of superficial medullary nodules the size of a pea; both kidneys were enlarged and presented numerous metastatic nodules the size of a cherry. The actual kidney parenchyma was to be seen in a few places only. No macroscopic change in the liver was observed, but on microscopical examination there were considerable collections of lymphoid cells around the central veins and in the interstitial tissue.

Several cases are reported by Turner.<sup>59</sup> In the first, the kidneys were enormous in size, owing to the infiltration with lympho-sarcomatous tissue. One weighed 19 and the other 19½ ounces. The glands under the jaw and the axillary glands were enlarged. There



were purpuric spots over the body, and ecchymoses in the pleura and pericardium. Another case in which the kidneys were much enlarged is reported by him, and there were multiple ecchymoses over the pericardium, peritoneum, dura-mater, optic discs and pia-mater. The microscopical appearances were similar to those in other cases, the growth in the liver following the portal spaces, and in the kidney it was intertubular, with a tendency to surround the glomeruli. Rosenstein<sup>62</sup> has published a case in which the superficial glands were enlarged, and metastases had occurred in the spleen, liver, kidneys and the right adrenal gland. In the kidneys there were atrophy and fatty degeneration of the epithelium of the tubules.

Packard<sup>60</sup> reports a case of a child 6 months old in which there were numerous subcutaneous tumors, and in which the thymus was large and indurated by buckshot-sized nodules scattered through it. There were masses of tumor surrounding the thoracic aorta, and metastases in the lungs and liver; the gastro-hepatic glands were enlarged, but the mesenterics were not, and the right adrenal gland was involved. Borlée<sup>61</sup> describes a colossal tumor of the lower jaw and neck in a man of 65. The axillary and inguinal glands were affected, and those of the root of the lungs and the bronchi also. The pancreas, mesenteric glands, cæcum and vermiform appendix were grown together into a tumor mass. Both kidneys were affected; in the knee of the corpus callosum was a tumor the size of a hazelnut.

From this brief review it will be seen that few if any structures of the body are free from the invasion of this affection. Although the place of origin is the lymphatic apparatus, and the cervical glands would seem, in a majority of cases, to be the earliest affected, Schulz<sup>54</sup> believes that several sets are simultaneously involved. However this may be, as Virchow and others have pointed out, the process sooner or later becomes heteroplastic and all structures are invaded indifferently.

A certain number of cases, on the other hand, proceed to their termination without my involvement of the superficial glands; and in still others, where there are lymphatic structures closely associated, one will be affected and the other not. In our cases, for example, with great involvements of the lymphatic apparatus of the intestine, the mesenteric glands escaped altogether.

The production of metastases in other organs, in the kidneys, liver, etc., is clearly due to infection by means of the blood current. The distribution of the affection in these organs is uniformly the same and follows the blood supply. In our first case, again, the tendency of the disease-process to appear about the blood-vessels of the submucous coat of the intestine, rather than the lymphatics, may account for the escape of the mesenteric glands and the infection of the liver and kidneys.

It is by no means clear why the kidneys should become affected through the blood and the lungs escape. This is seen to happen in many instances, and if the reported cases are studied there is seen to be a preference for the localization of the process in certain organs. Classing the spleen with the lymphatic glands—for it is quite as often involved as any set of glands—we have the liver, kidneys, intestines and the lungs susceptible in the order of their mention. Much more rarely are other organs affected, the central nervous system, skin, heart, ovaries, testicles, bone-marrow and adrenals. So far as the infection of the lungs is concerned, it is possible that the smaller size of the nodules which develop there and their relative inconspicuousness may account in part for the great difference observed.

But, on the other hand, it is evident that a large number of cases remain in which the process cannot be followed in its metastases as cancer can be, and it would seem to follow other laws. This difficulty has been present to the minds of other writers, and Schulz has emphasized the fact that the infection in lympho-sarcoma is not to be viewed as a metastasis in the usual sense, but to be regarded as the result of a virus diffused through the body, following an affection of the lymph glands.

From whatever side this affection is viewed, whether from its clinical history or its pathological anatomy (the latter being taken to include the histological structure, the alteration in the tissues produced by its presence, its mode of extension from one place to another, in the first instance from lymph glands to lymph glands, and then from the latter to other organs), we are met with the necessity of regarding it not so much in the light of a true tumor as of an infectious disease due to a specific micro-organism.

In conclusion I extend my sincere thanks to Professor Welch and Dr. Councilman for their advice and assistance while prosecuting this work.

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## EXPLANATION OF PLATES.

## PLATE V.

FIG. 1, Case 1.—One of the smaller nodules in the patch of Peyer, situated just above the valve. The mucous membrane, *A*, is observed to be thin and granular, the villi are degenerated and their outlines are represented by the dark lines. No crypts of Lieberkühn are to be seen, but a few gland spaces are still visible. The nodule, *B*, occupies the submucosa principally, and is continuous with the adjoining nodules. Leitz objective No. 1, ocular No. 1.

FIG. 2, Case 1.—The diffuse lymphoid infiltration of the mucous membrane and submucosa in the small intestine. The mucous membrane is indicated by a thin line of reticulated and granular tissue containing a few stained nuclei, *A*. The muscularis mucosæ is obscured. The lymphoid cells lie in a reticulum, *B*. There is a small collection of lymphoid cells in the circular muscular coat, *C*. Leitz objective No. 3, ocular No. 3.

FIG. 3, Case 1.—The necrotic mucous membrane and altered muscularis mucosæ in the small intestine. The villi, *A*, are degenerated, irregular in size and shape, and granular. Many have disappeared entirely; others are procumbent, and these are indicated by dark lines. The normal lymphoid cells between the glands are absent; the crypts of Lieberkühn are hyaline and necrotic, *B*, and some of the glands are devoid of cells. A few spindle-shaped nuclei and fine fibres are seen in the lower half of the mucous membrane. The muscularis mucosæ, *C*, is infiltrated with round cells; the submucosa is infiltrated, and they have extended into the muscle. Same magnification as last.

FIG. 4, Case 1.—Advanced atrophy of the mucous membrane. Just above the submucosa, *A*, there is a dense aggregation of spindle cells. The texture is looser above and more fibres are observed. The muscularis mucosæ is completely transformed. The submucosa is normal, *B*. Leitz objective No. 7, ocular No. 3.

## PLATE VI.

FIG. 1, Case 1.—From the sigmoid flexure of the colon, showing the glands in a state of comparative preservation, *A*. The



epithelium partly degenerated and some imperfect crypts are seen, *B*. In some glands the epithelium is completely gone, *C*. A slight lymphoid invasion of submucous coats seen at *D*.

FIG. 2, Case 2.—Small circumscribed nodule in the mucous membrane alone. Section parallel to long axis of the intestine. The mucous membrane degenerated. Crypts of Lieberkühn contain hyaline epithelium, the cells without nuclei. Leitz objective No. 3, ocular No. 1.

FIG. 3, Case 2.—Small circumscribed nodule in the ileum occupying the mucous membrane and submucosa. The degenerated mucous membrane, *A*, is converted into a granular, imperfectly reticulated structure. Villi and crypts are absent over a large area. Remnants of a villus at *B*, and a few remaining crypts at *C*. Leitz objective No. 3, ocular No. 1.

FIG. 4.—Constructed from both cases. Endothelial cell *A*, polynuclear leucocyte *B*, red-blood corpuscle *C*, for comparison with "peculiar bodies" *D*.



Fig. 1.

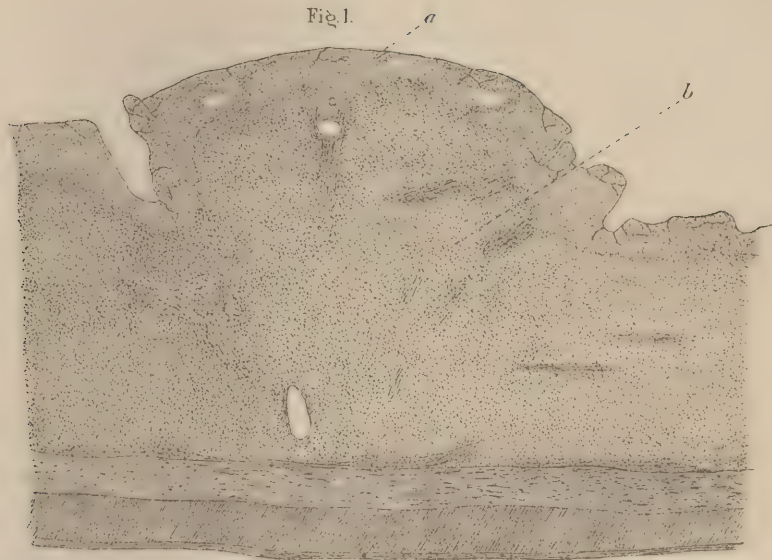


Fig. 2.

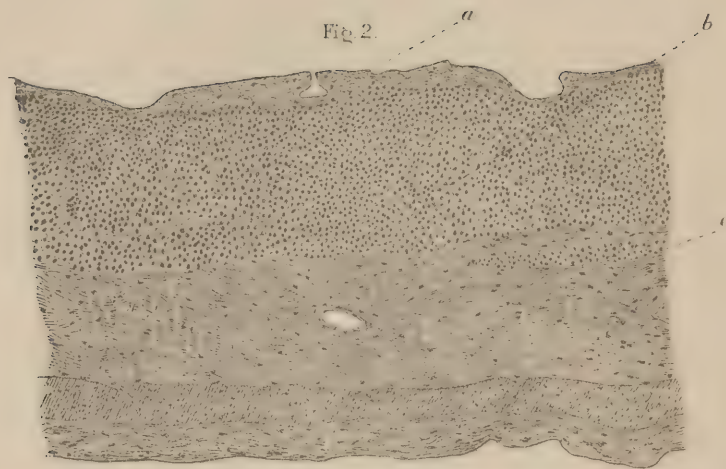


Fig. 3.

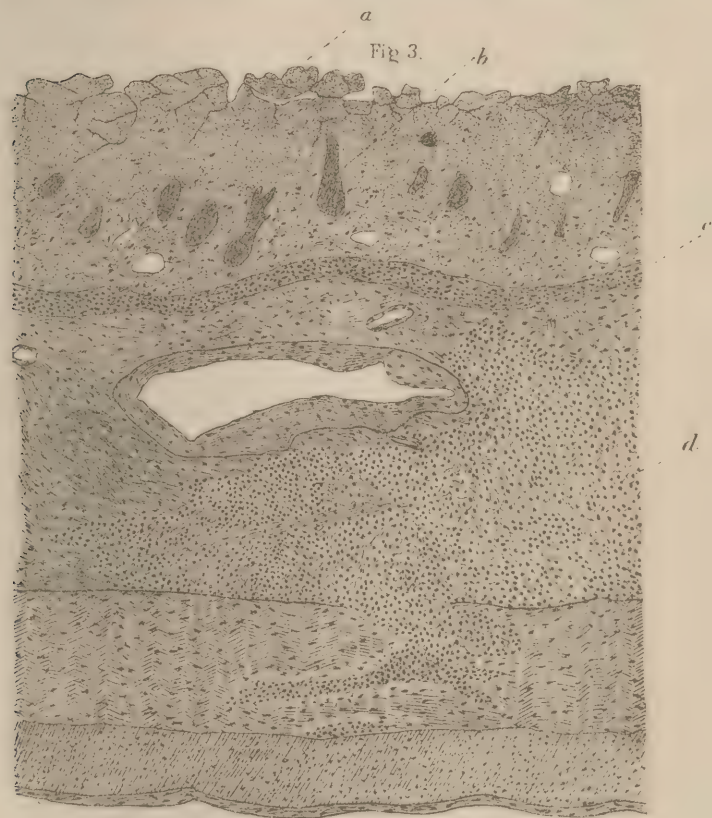


Fig. 4.

